

C-Reactive protein as a diagnostic tool in differential diagnosis of hypereosinophilic syndrome and antineutrophil cytoplasmic antibody–negative eosinophilic granulomatosis with polyangiitis



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Clinical Implications

- In asthmatic patients with eosinophilia and systemic manifestations, a low serum C-reactive protein level at diagnosis is suggestive of hypereosinophilic syndrome rather than eosinophilic granulomatosis with polyangiitis.

TO THE EDITOR:

The differential diagnosis of hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA) can be challenging in the context of asthma, blood eosinophilia, and systemic manifestations. EGPA (Churg-Strauss syndrome) differs from other antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides by the constant presence of asthma, blood eosinophilia, and presence of ANCAs (usually with myeloperoxidase [MPO] specificity, MPO/ANCAs) in only 30% or so of cases.^{1–3}

Patients with ANCAs are more likely to display a “vasculitis phenotype” and, conversely, a nonnegligible proportion of patients without ANCA reported in the largest series to date lacked histologic evidence of vasculitis.^{1–3} Moreover, the results of a recent placebo-controlled trial demonstrating the benefit of mepolizumab in a significant proportion of patients with EGPA with relapsing or treatment-refractory disease, further suggest that some patients with EGPA have an “eosinophilic phenotype” rather than a “vasculitis phenotype.”⁴

To date, the clinical and biological characteristics of HES versus EGPA have not yet been described in a large group of patients. To address this question, we performed a retrospective, observational, single-center study at Lille University Hospital. Both hospital discharge (*International Classification of Diseases, 10th Revision* codes) and laboratory databases were queried to screen all adult patients (aged 18 years or older) diagnosed and/or treated between 2006 and 2016 (see the [Methods](#) section in this article’s Online Repository at www.jaci-inpractice.org).

Of the 543 screened patients, 166 met our inclusion criteria (absolute eosinophil count [AEC], >1 G/L, and a positive MPO/ANCA assay and/or manifestations related to organ damage and/or dysfunction attributable to tissue hypereosinophilia, excluding asthma and ear, nose, and throat manifestations without any exclusion criterion; see [Figure E1](#) in this article’s Online Repository at www.jaci-inpractice.org). Given the substantial clinical and biological overlap between these 2 diseases, we compared the characteristics of patients without using the conventional classification criteria of EGPA and HES.^{5,6} Included patients were classified as follows: 18 MPO/ANCA+ patients with persistent asthma (Asth+ANCA+), 65 MPO/ANCA– patients with persistent asthma (Asth+ANCA–), and 83 MPO/ANCA– patients without asthma (Asth–ANCA– patients). No patient was positive for anti-PR3 and no asthma-free patient tested positive for ANCAs. The patients’ main demographic, clinical, and biological characteristics at diagnosis are summarized in [Table I](#).

In the Asth+ANCA– group, 97%, 58%, and 34% of the patients met the criteria for HES,⁵ the American College of Rheumatology criteria for EGPA,⁶ and the Groupe d’Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and European Respiratory Society taskforce (GERMOP/ERS) criteria for EGPA,³ respectively, which highlights the overlap between the conventional classification criteria ([Table I](#)). Finally, 51% of Asth+ANCA– patients met the criteria for hypereosinophilic asthma with systemic (nonvasculitic) manifestations, which is in line with the recent report on the GERMOP/ERS cohort, in which 59% of ANCA– patients with asthma met these criteria.³

As reported by others,^{1–3} Asth+ANCA– patients presented significantly less hematuria + proteinuria (>0.2 g/d; 2% vs 22%; $P = .021$) and mononeuritis multiplex (17% vs 61%; $P = .001$) than Asth+ANCA+ patients, and they also showed a nonsignificant trend toward a lower frequency of definite vasculitis (25% vs 56%; $P = .06$) and alveolar hemorrhage (3% vs 22%; $P = .054$).

Ninety-nine percent of Asth–ANCA– patients met the criteria for HES, and none of them met the criteria for EGPA in absence of asthma. Moreover, their clinical profile was similar to that of the international cohort of 188 patients with HES, 64%, 54%, and 37% of whom developed dermatologic, pulmonary, and gastrointestinal manifestations, respectively (vs 69%, 44%, and 38% in our study).⁷ Consequently, we considered Asth–ANCA– patients to be our reference set for HES diagnosis. Conversely, MPO/ANCAs being the strongest biomarker for EGPA, Asth+ANCA+ patients were chosen as the reference set for EGPA diagnosis.

TABLE I. General characteristics of patients with blood eosinophilia (>1 G/L) and systemic manifestations

Characteristic	Asth + ANCA + (n = 18)	P value*	Asth + ANCA – (n = 65)	P value*	Asth – ANCA – (n = 83)
Sex, male/female	11/7	NS	24/41	.025	49/34
Age (y)	59 (49; 63)	NS	48 (43; 58)	.002	60 (39; 72)
Criteria for HES		NS			
HES criteria	18 (100%)	NS	63 (97%)	NS	82 (99%)
Blood eosinophilia ≥ 1.5 G/L at ≥ 2 examinations	18 (100%)	NS	63 (97%)	NS	80 (96%)
Tissue eosinophilia	5 (28%)	.003	47 (72%)	NS	63 (76%)
Clonal eosinophilia and/or myeloproliferative disorder	0	NS	1 (2%)	NS	9 (11%)
Abnormal circulating T cells (lymphocytic variant HES)	0	NS	2 (3%)	NS	7 (8%)
Criteria for EGPA		NS			
≥ 4 of the 6 1990 ACR criteria	15 (83%)	NS	38 (58%)	<.001	1 (1%)
GERMOP/ERS revised nomenclature					
EGPA criteria (polyangiitis)	18 (100%)	<.001	22 (34%)	NA	NA
Definite vasculitis	10 (56%)	.06	16 (25%)	<.001	2 (2%)
Strong surrogate of vasculitis	0	NS	0	NS	0
Mononeuritis multiplex	11 (61%)	.001	11 (17%)	.075	4 (5%)
MPO/ANCA	18 (100%)		0		0
Hypereosinophilic asthma with systemic (nonvascularitic) manifestations	NA	NA	33 (51%)	NA	NA
General manifestations					
Fever $>38^{\circ}\text{C}$	7 (39%)	NS	20 (31%)	<.001	2 (2%)
Asthenia	14 (78%)	NS	42 (65%)	.003	30 (36%)
Myalgia	6 (33%)	NS	11 (17%)	NS	7 (8%)
Arthralgia	7 (39%)	NS	18 (28%)	NS	14 (17%)
Lung manifestations					
History of asthma	NA		NA		9 (11%)
Persistent asthma at diagnosis	18 (100%)	NS	65 (100%)	NA	NA
Duration of asthma at diagnosis (y)	4.5 (1.25; 9.75)	NS	4 (1.5; 19.5)	NA	NA
Allergic asthma	4 (22%)	NS	24 (37%)	NA	NA
Lung infiltrates	9 (50%)	NS	34 (52%)	<.001	11 (13%)
Pleural effusion	2 (11%)	NS	13 (20%)	NS	11 (13%)
Alveolar hemorrhage	4 (22%)	.054	2 (3%)	NS	0
Eosinophilic count $\geq 25\%$ in bronchoalveolar lavage	3 (17%)	NS	10 (15%)	NS	7 (8%)
ENT manifestations		NS			
Chronic rhinosinusitis	15 (83%)	NS	51 (78%)	<.001	19 (23%)
Nasal polyposis	9 (50%)	NS	35 (54%)	<.001	7 (8%)
Cardiac manifestations		NS			
Myocarditis	0	NS	9 (14%)	.015	1 (1%)
Myocardial infarction due to coronary arteritis	0	NS	1 (2%)	NS	0
Pericarditis	2 (11%)	NS	16 (25%)	.005	5 (6%)
Endomyocardial fibrosis	0	NS	2 (3%)	NS	2 (2%)
Deep venous thrombosis/pulmonary embolism	0	NS	3/1 (5%/2%)	NS	6/1 (7%/1%)
Renal manifestations					
Hematuria + proteinuria > 0.2 g/d	4 (22%)	.021	1 (2%)	NS	0
Biopsy-proven necrotizing or crescentic glomerulonephritis	2 (11%)	NS	1 (2%)	NS	0
Creatinine > 150 $\mu\text{mol/L}$	1 (6%)	NS	1 (2%)	NS	0
Gastrointestinal manifestations		NS			
Abdominal pain	4 (22%)	NS	18 (28%)	NS	22 (27%)

(continued)

TABLE I. (Continued)

Characteristic	Asth+ANCA+ (n = 18)	P value*	Asth+ANCA- (n = 65)	P value*	Asth-ANCA- (n = 83)
Diarrhea	1 (6%)	NS	14 (22%)	NS	19 (23%)
Pancreatitis	0	NS	2 (3%)	NS	4 (5%)
Eosinophilic gastroenteritis (biopsy-proven)	0	NS	7 (11%)	NS	13 (16%)
Ischemic colitis	0	NS	0	NS	2 (2%)
Ascites	0	NS	3 (5%)	NS	4 (5%)
Neurologic manifestations				NS	
Mononeuritis multiplex	11 (61%)	.001	11 (17%)	.075	4 (5%)
Distal polyneuropathy	1 (6%)	NS	11 (17%)	NS	5 (6%)
Inflammatory lesions of cerebral white matter	0	NS	0	NS	3 (4%)
Cerebral vasculitis	1 (6%)	NS	3 (5%)	NS	1 (1%)
Ischemic stroke (without vasculitis)	1 (6%)	NS	5 (8%)	NS	5 (6%)
Cutaneous manifestations		NS			
Palpable purpura	5 (28%)	NS	10 (15%)	<.001	0
Digital necrosis	0	NS	0	NS	1 (1%)
Splinter hemorrhage	0	NS	1 (2%)	NS	1 (1%)
Livedo racemosa	1 (6%)	NS	0	NS	1 (1%)
Erythematous papules, plaques, and/or nodules	0	NS	14 (22%)	.005	39 (47%)
Urticaria	0	NS	9 (14%)	NS	15 (18%)
Angioedema	1 (6%)	NS	8 (12%)	NS	8 (10%)
Biological characteristics					
AEC (G/L)	6 (4.2-11.3)	NS	4.2 (2.4-10.6)	.07	2.7 (2-6.2)
Eosinophils > 10% of leukocytes	17 (94%)	NS	61 (94%)	NS	82 (99%)
Elevated serum tryptase†	0	NS	4 (12%)	NS	10 (15%)
Elevated serum IgE†	6 (75%)	NS	42 (74%)	NS	34 (61%)
Elevated serum vitamin B ₁₂ †	0	NS	1 (2%)	NS	6 (11%)
Serum CRP (mg/L)‡	76.5 (23-131)	.03	35 (8-73)	<.001	3 (0-12)

ACR, American College of Rheumatology; ENT, ear nose, and throat; MPO, myeloperoxidase; NA, not applicable; NS, nonsignificant.

Continuous variables are quoted as the median (interquartile range), and categorical variables are quoted as the number (percentage).

*Adjusted P values are given for intergroup comparisons—adjacent columns—of each variable. Significant comparisons are in bold.

†The serum tryptase level was available for 3/34/66 patients in Asth+ANCA+, Asth+ANCA-, Asth-ANCA- patients, respectively, with data on IgE in 8/57/56 and data on vitamin B₁₂ in 8/42/55.

‡The serum CRP level was available without confounding factors for 16/59/77 patients in Asth+ANCA+, Asth+ANCA-, Asth-ANCA- patients, respectively. The mean ± SD CRP levels were 92.6 ± 49.6 mg/L in Asth+ANCA+ and 53.2 ± 54.2 mg/L in Asth+ANCA-.

The highest median (interquartile range) serum C-reactive protein (CRP) level was reported in Asth+ANCA+ patients (76.5 mg/L [58-130]) (Figure 1, A) and was similar to that measured in patients with MPO/ANCA+ with granulomatosis with polyangiitis or microscopic polyangiitis (85 [54-130]; $P = .78$) (Figure 1, B). This suggests that a high CRP level is consistent with ANCA+ systemic vasculitis. The median serum CRP level was higher in Asth+ANCA+ patients than in Asth+ANCA- patients (35.0 mg/L [8-73]; $P = .028$). The same observation was previously made in the French Vasculitis Study Group Cohort, with mean ± SD serum CRP levels of 78.7 ± 62.4 and 58.5 ± 60.1 mg/L in ANCA+ and ANCA- patients, respectively ($P = .04$).²

The lowest median serum CRP level was reported in Asth-ANCA- patients (3.0 mg/L [0-12]) (Figure 1, A) and was similar to those recorded in patients with isolated eosinophilic asthma with AEC of greater than 1 G/L (0 [0-5.2]; $P = .11$) and in patients with asymptomatic unexplained eosinophilia with AEC of greater than 1 G/L (0 [0-3]; $P = .84$) (Figure 1, C). This suggests

that a normal or slightly elevated CRP level is expected in a high proportion of cases in which a diagnosis of EGPA can be easily ruled out (ie, no asthma and/or no systemic manifestations).

Both serum CRP values in Asth+ANCA+ and Asth-ANCA- groups differed significantly from the median serum CRP level of Asth+ANCA- group (35.0 mg/L [8-73]; $P < .001$ in a Kruskal-Wallis test).

We next decided to evaluate the diagnostic value of the serum CRP level in Asth+ANCA- patients (in which it is the most challenging to discriminate between HES and EGPA). We considered the Asth+ANCA+ group as the reference set for EGPA and the Asth-ANCA- group as the reference set for HES. On the receiver operating characteristic curve, the area under the curve (95% CI) for serum CRP was 0.966 (0.907-0.993) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). According to the Youden index, the best cutoff value was less than 36 mg/L; this yielded a sensitivity of 94.8% (87.2-98.6), a specificity of 93.7% (69.8-99.8), and a positive predictive value of 98.6% (91.6-99.8) for the diagnosis of HES.

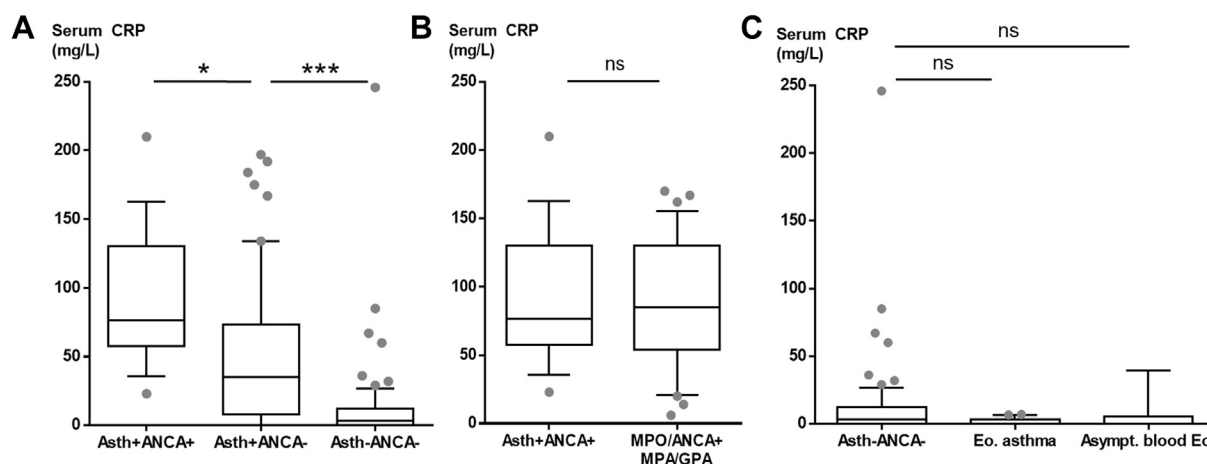


FIGURE 1. CRP levels in the study groups (A) and control groups (B and C). Asth+ANCA+ (n = 16); Asth+ANCA- (n = 59); Asth-ANCA- (n = 77); *Asympt. blood Eo.*, Asymptomatic unexplained blood eosinophilia (n = 19); *Eo. asthma*, isolated eosinophilic asthma (n = 22); *MPO+ MPA/GPA*, MPO/ANCA+ patients with granulomatosis with polyangiitis or microscopic polyangiitis (n = 35); *ns*, nonsignificant. Boxes: median (interquartile range); error bars: 10th-90th percentiles. * $P = .028$. *** $P < .001$.

Interestingly, Asth+ANCA- patients with a serum CRP level of 36 mg/L were less likely to meet both the American College of Rheumatology criteria for EGPA (37% vs 83%; $P < .001$) and the GERMOP/ERS criteria for EGPA (13% vs 55%; $P < .001$), including definite vasculitis (10% vs 38%; $P = .012$), purpura (3% vs 28%; $P = .012$), and mononeuritis multiplex (7% vs 31%; $P = .016$) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

In the present study, serum CRP levels collected at diagnosis and in absence of confounding factors (such as corticosteroids) differ between Asth+ANCA+, Asth+ANCA-, and Asth-ANCA- patients. A previous study unsuccessfully tried to differentiate between EGPA and HES by considering levels of CRP and many other biomarkers; this failure was probably due to the small number of patients, and the fact that 60% of patients were taking corticosteroids at the time of evaluation.⁸ The disparity between the literature data and our results might be due to the heterogeneity of eosinophilic disorders encompassed within the diagnosis of "EGPA," and notably HES in which a low serum CRP level is expected at diagnosis and during follow-up.

To conclude, in asthmatic patients with eosinophilia and systemic manifestations, our results suggest that a low serum CRP level at diagnosis is suggestive of HES rather than EGPA.

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ONLINE REPOSITORY

Methods

Patients. We performed a retrospective, observational, single-center study at Lille University Hospital, which is a member of the French National Reference Centre network for HES. Both hospital discharge and laboratory databases were queried with relevant *International Classification of Diseases, 10th Revision (ICD-10)* codes, to screen all adult patients (aged 18 years or older) diagnosed and/or treated in 1 of the clinical departments at Lille University Hospital between 2006 and 2016. The *ICD-10* codes used were M301 (periarteritis with pulmonary involvement, for EGPA), J82 (pulmonary eosinophilia), D475 (chronic eosinophilic leukemia), and D721 (eosinophilia). Next, to identify additional patients, the databases of the immunology and hematology laboratories were screened for requests for lymphocyte immunophenotyping (for HES_L) and tests for FIP1-like1 platelet-derived growth factor receptor α gene fusion. We also analyzed all patients with a positive MPO/ANCA assay (ANCA+): the latter was defined as a perinuclear pattern in an indirect immunofluorescence assay (Nova Lite kits, Inova Diagnostics, San Diego, Calif; or Europlus kits, Euroimmun, Bussy-Saint-Martin, France), followed by the detection of anti-MPO antibodies in a specific ELISA (Inova Diagnostics) or BioPlex Vasculitis Panel (Biorad, Marne-la-Coquette, France). All demographic, clinical, laboratory, and histopathological data were systematically collected from medical charts using a standardized form. All doubtful cases were reviewed by experienced physicians in the fields of eosinophilic disorders (G.L.) and/or an experienced respiratory physician (C.C.).

Patients were included if they met the following inclusion criteria: (1) blood eosinophilia greater than $1.0 \times 10^9/L$, and (2) a positive MPO/ANCA assay and/or manifestations related to organ damage and/or dysfunction attributable to tissue hyper-eosinophilia (excluding asthma and ear nose, and throat [ENT] manifestations). With the exception of HES_L, patients with other known etiologies for reactive eosinophilia, for example, infectious, neoplastic, or autoimmune diseases (other than EGPA), hematological malignancies, drug hypersensitivity reactions, hypoadrenalism, and IgG₄-related diseases were excluded (see [Figure E1](#) for further details). Patients with isolated eosinophilic asthma (ie, with no systemic manifestations) were also excluded.

Study design. Patients with blood eosinophilia and systemic manifestations were divided into 3 study groups: Asth+ANCA+ patients, Asth+ANCA− patients, and Asth−ANCA− patients. Patients' clinical and biological characteristics were compared according to patient subsets.

In the second part of our study, we focused on the diagnostic value of serum CRP levels in the 3 study groups, relative to 3 control groups. We compared Asth+ANCA− patients (considered as the reference set for EGPA diagnosis) with MPO/ANCA+ patients with a diagnosis of granulomatosis polyangiitis (Wegener's granulomatosis) or microscopic polyangiitis, whereas Asth−ANCA− patients (considered as the reference set for HES diagnosis) were compared with (1) eosinophilic patients with isolated asthma and (2) asymptomatic patients with unexplained eosinophilia greater than $1 \times 10^9/L$. As for the study patients, the control patients were included in the CRP analysis only if there were no confounding factors at diagnosis (such as another inflammatory disorder, a concomitant infectious disease, or the

initiation of corticosteroid treatment before the first CRP assay). Finally, within the group of Asth+ANCA− patients, we compared the characteristics of individuals with low versus high serum CRP levels.

Definitions. All diagnoses were reassessed by the investigators (A.L., C.C., G.L.). We applied the standard diagnostic criteria for HES, the 1990 American College of Rheumatology criteria for EGPA, and the GERMOP/ERS criteria for EGPA and HASM:

- Diagnostic criteria for HES^{E1}
 - Peripheral blood hypereosinophilia greater than $1.5 \times 10^9/L$ (on 2 examinations at least 1 month apart, except in case of progressing, life-threatening end-organ damage requiring immediate therapy), and
 - Organ damage and/or dysfunction attributable to tissue eosinophilia as defined in the 2012 Consensus proposal on criteria and classification of eosinophilic disorders and related syndromes referenced above,^{E1} and
 - Exclusion of other disorders or conditions as the major cause of organ damage.

When no biopsy was available, an organ damage and/or dysfunction were finally considered as an HES manifestation if its evolution was consistent with the evolution of other HES manifestations and/or of blood eosinophilia.

- The 1990 American College of Rheumatology diagnostic criteria for EGPA (≥ 4 out of 6 criteria required)^{E3}
 - Asthma
 - Eosinophilia (more than 10% of the peripheral blood leukocytes)
 - Paranasal sinus abnormalities
 - Pulmonary infiltrates, nonfixed
 - Extravascular eosinophils
 - Neuropathy
- GERMOP/ERS diagnostic criteria for vasculitis in EGPA: 1 or more of the following criteria in hypereosinophilic asthma (eosinophils $\geq 1.5 \times 10^9/L$ and/or $\geq 10\%$ of leukocytes)^{E2}
 - Definite vasculitis:
 - 1 biopsy-proven necrotizing vasculitis of any organ, or
 - 2 necrotizing glomerulonephritis or crescentic glomerulonephritis (biopsy proven), or
 - 3 alveolar hemorrhage (defined as bloody bronchoalveolar lavage return with compatible opacities on chest X-ray and/or high-resolution computed tomography), or
 - 4 palpable purpura, or
 - 5 myocardial infarction due to proven coronaritis (related to the systemic disease, eg, nonatheromatous coronary stenosis at coronarography or myocardial infarction without coronary atherosclerosis)
 - Strong surrogate criteria for vasculitis:
 - 1 hematuria associated with red casts or greater than or equal to 10% dysmorphic erythrocytes, or hematuria and 2+ proteinuria on urinalysis (related to the systemic disease, no biopsy) and
 - 2 any organ manifestation other than ENT or bronchopulmonary manifestation associated with a biopsy demonstrating leukocytoclastic capillaritis and/or eosinophilic infiltration of the arterial wall
 - Mononeuritis multiplex

- ANCA on an ELISA with at least 1 extrathoracic, non-ENT manifestation of disease
- GERMOP/ERS diagnostic criteria for hypereosinophilic asthma with systemic (nonvasculitic) manifestations^{E2}
 - asthma
 - blood eosinophils superior at 1.5 G/L
 - any systemic manifestation other than definite polyangiitis or surrogate of vasculitis or mononeuritis
 - absence of ANCA

Ethical statement. Patients included via routine consultations at Lille University Hospital were informed that their clinical data could be used for research purposes and were free to refuse this use. In line with the regulations set out by the French National Data Protection Commission (declaration number of the present study: DEC16-263), written informed consent was not requested for this noninterventional study.

Statistical analysis. Analyses were performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC). Continuous variables are quoted as the median (interquartile range), and categorical variables are quoted as the number

(percentage). For comparisons of categorical variables, we used a chi-square test or Fisher exact test, as appropriate. Sidak's correction was applied for intergroup comparisons for each variable when more than 2 groups were concerned (multiple comparisons). For comparisons of continuous variables, we used Student test or the Mann-Whitney test, as appropriate. For multiple comparisons, we used the Kruskal-Wallis test with Dunn's post hoc test.

A receiver operating characteristic curve was plotted for serum CRP levels, and the area under the curve was calculated to discriminate between ANCA+ asthmatic patients (used as the reference set for EGPA diagnosis) and asthma-free patients (used as the reference set for HES diagnosis). The best cutoff value was chosen according to the Youden index calculation, which defines the maximum potential effectiveness of a biomarker when equal weight is given to sensitivity and specificity. The positive predictive value and the negative predictive value were calculated on the basis of the target condition's prevalence in the included population.

All tests were 2-tailed. The threshold for statistical significance was set to $P < .05$.

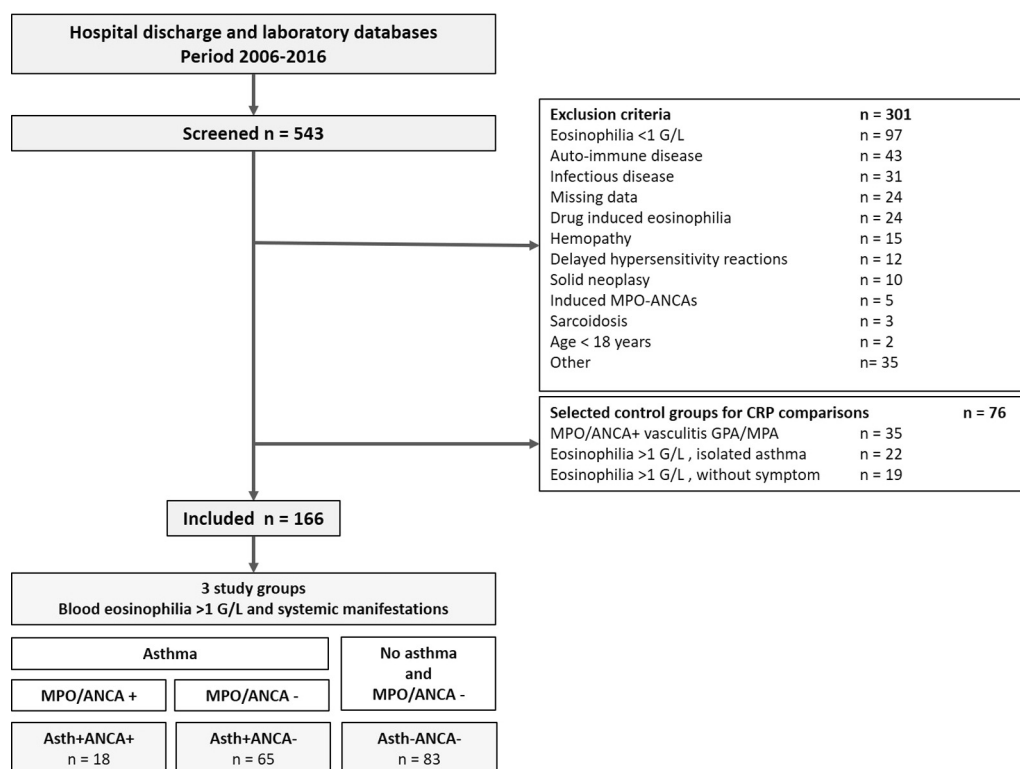


FIGURE E1. Study flowchart. GPA, Granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

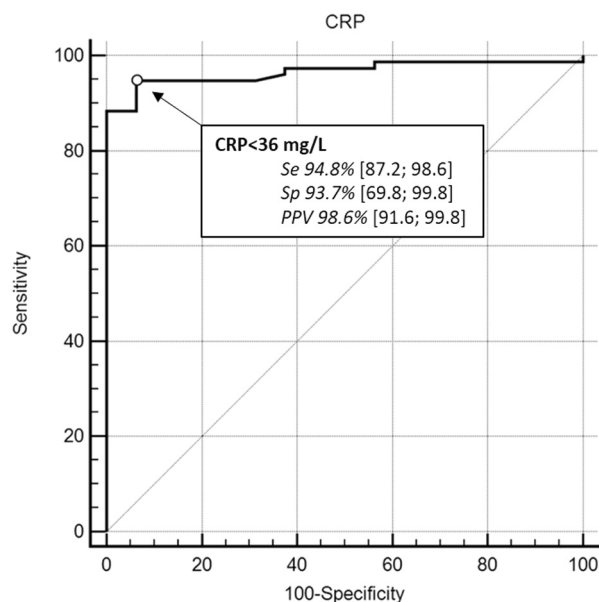


FIGURE E2. ROC curve for serum CRP in Asth+ANCA+ patients (the reference group for EGPA diagnosis) and Asth–ANCA– patients (the reference group for HES diagnosis). The performance level of the cutoff CRP (<36 mg) is given for the diagnosis of HES (95% CI). PPV, Positive predictive value; Se, sensitivity; Sp, specificity.

TABLE E1. Characteristics of Asth+ANCA– patients, as a function of the serum CRP level

Characteristic, n (%)	CRP < 36 mg/L (n = 30)	CRP > 36 mg/L (n = 29)	P
Hypereosinophilic asthma with systemic (nonvasculitic) manifestations,* n (%)	20 (67)	10 (34)	.013
≥4 of the 6 1990 ACR criteria	11 (37)	24 (83)	<.001
EGPA criteria (polyangiitis)*	4 (13)	16 (55)	<.001
Definite vasculitis*	3 (10)	11 (38)	.012
Palpable purpura	1 (3)	8 (28)	.012
Mononeuritis multiplex	2 (7)	9 (31)	.016
Distal polyneuropathy	3 (10)	8 (28)	.083
Myocarditis	2 (7)	7 (24)	.06
Alveolar hemorrhage	1 (3)	0	NS
Biopsy-proven necrotizing or crescentic glomerulonephritis	0	1 (3)	NS
Cerebral vasculitis	1 (3)	1 (3)	NS
Myocardial infarction due to coronary arteritis	0	1 (3)	NS

ACR, American College of Rheumatology.

Categorical variables are quoted as the number (percentage).

*According to GERMOP/ERS revised nomenclature.

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